REYE'S SYNDROME

INFECTIOUS DISEASE RESEARCH

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Reye's syndrome is one of man's modern medical mysteries. It is a life-threatening disease that develops rapidly in some children usually following an acute viral infection. With the highest rate of incidence reported in the United States, Canada, and Thailand, Reye's syndrome has occurred in at least 21 countries and has affected children in rural, suburban, and urban areas.

Although it is not a common illness (in the United States it is estimated that 1 to 2 cases occur every year per 100,000 children under the age of 18) scientists are conducting intensive research to discover the cause(s) of this potentially fatal disease and the best methods of diagnosing and treating it.

First described in 1963 by R.D.K. Reye, an Australian pathologist, Reye's syndrome is characterized by acute encephalopathy (swelling of the brain) and fatty degeneration of the liver. The liver in a Reye's syndrome patient generally contains an unusually large amount of fat distributed in small droplets. In addition, the liver's functions become impaired, and there are structural alterations of its mitochondria—the small, spherical components of cells that release stored energy in food needed for the body's activities. These changes in mitochondria are also found in the muscle and brain tissues. The brain swells, and the excessive build-up of pressure inside the skull results in brain dysfunction, and possibly death.

Symptoms

Researchers have established a clear association between the development of Reye's syndrome and outbreaks of Influenza B, Influenza A, and varicella (chickenpox). In a typical case, a child will have either influenza or chickenpox, most likely during the winter or early spring months when epidemics of these diseases normally occur. The child seems to be recovering from this viral disorder, but then will experience the abrupt onset of persistent and intractable vomiting, usually the first sign of Reye's syndrome. The child may undergo changes in mental state, becoming listless, lethargic, and disoriented, or sometimes becoming hostile or unusually annoyed if spoken to or touched. Other symptoms may include combativeness, inability to recognize family members, incessant moaning or screaming, and twitching and jerking. Within a short period, measured in minutes or hours, the child may become unconscious, and may progress to a deep coma and possibly death. If untreated, the period from the start of vomiting to death is 3 to 5 days.

Epidemiology

The fatality rate for Reye's syn-

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drome is not easy to ascertain since the disease is difficult to diagnose and mild cases may not be reported. Furthermore, a standardized definition of mild cases of Reye's syndrome has not yet been developed. Increased awareness of the disease on the part of physicians and hospital staff has led to greater voluntary reporting. Between December 1, 1979 and November 30, 1980, the Centers for Disease Control received 548 confirmed reports of Reye's syndrome occurring in 44 states and Washington, D.C. The incidence is probably higher, and estimates of 600 to 1,200 cases per year have been made. Approximately 20 percent of the cases reported through national surveillance are fatal.

Cases of Reye's syndrome are divided almost equally among boys and girls. A racial breakdown indicates that white children are affected at a higher rate, although Reye's syndrome also occurs in blacks, Hispanics, Asians, and other ethnic groups. Among babies under the age of 1 year, black infants have a higher incidence of Reye's syndrome, yet black children over the age of 1 seem less susceptible to developing the disease than white children.

Causative Factors

The factors which interact with the initial viral infection to trigger Reye's syndrome in some children have not yet been identified. Some reports have suggested an association between Reye's syndrome and insecticides.

Ingestion of aflatoxin, a toxin produced by fungal molds sometimes found in stored agricultural products, has also been suggested as a cause of Reye's syndrome since experimental use of aflatoxin in macaque monkeys produced liver lesions similar to those found in children with Reye's syndrome. However, there is no strong epidemiological basis to implicate either insecticides or aflatoxin.

Recent observations suggest a possible link between the development of Reye's syndrome and the use of salicylates (aspirin) during the preceding viral infection. Studies reported by the Centers for Disease Control showed higher use of aspirin among children who were hospitalized for Reye's syndrome than among matched children who had a similar viral illness but did not develop Reye's syndrome. The majority of the children who were given aspirin took no more than is normally recommended. In issuing a policy statement on the subject, the American Academy of Pediatrics emphasized that the relationship between aspirin and Reye's syndrome is an association only, and causation has not been established. Further studies are needed to explain this association. The Centers for Disease Control, however, has urged caution in giving aspirin to control fever in children who develop influenza-like illnesses or chickenpox.

Diagnosis

The successful management of Reye's syndrome is facilitated by early diagnosis. If detected and treated in its beginning stages, most Reye's syndrome patients can, and do, recover completely.

Children who develop persistent vomiting following recovery from a viral illness and who develop listlessness, irritability, disorientation, or increasing lethargy, should receive prompt medical attention. A physician will perform laboratory tests and a case history may be taken to consider the possibility of other illnesses whose symptoms mimic those of Reye's syndrome.

A diagnosis of Reye's syndrome is usually made if there is an elevated blood ammonia level, and if acute noninflammatory encephalopathy is present with either fatty changes in the liver or excessive increases in two enzymes called SGOT and SGPT. SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) are enzymes normally present in the liver, which are released into serum in high concentrations as a result of injury to the liver cells. The tests that are performed on a child also indicate whether an excessive level of ammonia is present in the blood, an indicator of mitochondrial injury within the liver, which is typical of Reye's syndrome patients.

Treatment

Although there is no known cure for Reye's syndrome, intensive supportive care in a hospital with intensive care facilities and staff experienced in treating Reye's syndrome can often reverse the course of the disease.

Once a diagnosis of Reye's syndrome has been made, treatment is concentrated on the control of brain swelling and intracranial pressure through the use of drugs and monitoring measures. Even with this aggressive therapy, some children who recover from Reye's syndrome may suffer permanent brain damage. Although treatments may vary, the prognosis for children with Reye's syndrome is improving. This may be attributable in part to the fact that more diagnoses of Reye's syndrome are made before children reach advanced stages of the disease, physicians now have more experience in treating the disease, and treatment is more aggressive.

Research

The National Institutes of Health is sponsoring research efforts to identify the causes of Reye's syndrome, develop methods of treatment and/or prevention, improve methods of diagnosis, and identify which children might be at high risk. Because Reye's syndrome research transcends the areas of epidemiologic, neurologic, and metabolic studies, NIH-supported investigations are multi-institutional to provide the broad coverage needed in the study of this disease. The institutes conducting Reye's syndrome research include the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), the National Institute of Child Health and Human Development (NICHD), and the Division of Research Resources (DRR).

Epidemiologic studies are being conducted to determine if viruses, aflatoxins, insecticides, or pesticides may play a role in the development of Reye's syndrome. Researchers are also working on improving existing Influenza A and B vaccines, developing new ones, and studying varicella vaccines. If influenza and varicella infections can be controlled and eventually prevented, Reye's syndrome may not occur in the aftermath of these epidemics.

Five general Clinical Research Centers located at universities throughout the country also receive support from NIH to conduct research on Reye's syndrome. Their research focuses on such areas as determining whether any metabolic defects remain in the survivors of Reye's syndrome, finding methods to reduce the high levels of ammonia that occur during Reye's syndrome, and understanding the mechanisms involved in the disease that produce the severe brain swelling. One recently initiated study has been undertaken to evaluate the neurological, psychological, and educational abilities of children who have survived Reye's syndrome.

The development of animal models and the study of biochemical correlates are also topics of interest to scientists. Other grantees are searching for a serum factor that might be responsible for destroying the mitochondria in children with Reye's syndrome. Working with rat liver mitochondria incubated with serum from Reye's syndrome patients, these researchers are trying to ascertain what substance in the serum could be the cause of the structural and functional alterations in the mitochondria.

In addition to national surveillance, the Centers for Disease Control is studying the possible role of specific viruses, aflatoxins, and medications. The Centers for Disease Control also conducts investigations of Reye's syndrome outbreaks when they occur in the United States.

Reye's syndrome is receiving increased national attention. The National Institutes of Health sponsored a consensus development conference on Reye's syndrome in March, 1981 which brought together scientists and investigators from various disciplines and concerned citizens. A full copy of the consensus summary on Reye's syndrome may be obtained by writing to:

National Institutes of Health
Office for Medical Applications of Research
Bldg. 1,
Rm. 216
Bethesda, Maryland 20205

Several private organizations also are actively concerned with Reye's syndrome. For additional information, write to:

best copy available

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